

Research Article

Influence of Uric Acid Levels on Pegylated-Interferon plus Ribavirin Therapy in Patients with Chronic Hepatitis C

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- Steatosis

Abstract

Introduction: It was aimed in this study to evaluate influence of uric acid levels on pegylated-interferon alpha (PEG-IFN- α) 2a/2b plus ribavirin therapy in patients with chronic hepatitis C.

Methods: A total of 165 chronic hepatitis c patients with ages ranging from 20 to 75 years having pre- and post-treatment serum uric acid and HCV-RNA (0, 12, 24, 48 and 72 weeks) levels available were included in the study. These parameters were assessed according to the groups based on response to therapy (sustained virologic response -SVR, relapse and non-responders).

Results: Of the 165 patients, 28 were excluded from hyperuricemia analyses owing to lack of uric acid levels and/or liver biopsies. Of the 137 included, 117 had no hyperuricemia while 20 did (cut-off levels were 7 and 6 mg/dL in males and female, respectively). In univariate analyses, no statistically significant association was established between hyperuricemia and age, waist circumference, HOMA-IR score, sustained virologic response, fibrosis and histologic activity index (p values were 0,61; 0,115; 0,437; 0,645; 0,235 and 0,166; respectively). However, significant association was found between hyperuricemia and body mass index, hypertension, existence of metabolic syndrome and grade of steatosis (p values were 0,045; 0,04; 0,045; 0,007; respectively). No significant relevance was noted between hyperuricemia and the parameters in multivariate analyses.

Conclusion: There has been detected a significant association between hyperuricemia and steatosis in patients with chronic hepatitis C. However, no influence on therapy has been found with regard to uric acid levels. Multicenter studies are required to enlighten this metabolic chaos.

INTRODUCTION

It is reported in literature that approximately 3% of world population- which equals to 170 - 200 million people - is infected with hepatitis c virus (HCV) [1]. Our country being moderate endemic in terms of HCV has a HCV prevalence of 1-3% [2]. Peak age group of HCV is thought to be 20-39 while it is 30-49 for chronic hepatitis C (CHC). The majority of CHC cases are anicteric and asymptomatic [3]. HCV is responsible for 20% of acute viral hepatitis, 70% of chronic viral hepatitis, 40% of viral hepatitis ending with cirrhosis, 60% of hepatocellular cancer (HCC) and 30% of cases requiring liver transplantation in developed countries [4].

It was interferon monotherapy that was the first agent used

in treatment of CHC in 1990. In 1998, interferon and ribavirin combination was shown to be more effective than interferon alone. Efficacy of interferon alfa was limited due to fast clearance and short half-life. Thus, pegylated forms were developed to extend the short half-life. Following head to head comparisons, PEG-IFN & ribavirin combination started to be the standard therapy. Response rates of 50-60% and 80-90% were achieved with this therapy in genotype 1 and genotype 2 & 3, respectively [5-7]. This combination therapy may cause flu-like symptoms, fatigue, hair loss, anemia, leucopenia and thrombocytopenia. Although less frequently; acute psychosis, convulsions, autoimmune reactions, hyperthyroidism and hypothyroidism may also be seen [8]. Early discontinuation of therapy may come up owing to side effects in 10-20% of cases [9].

METHODS

A total of 165 chronic hepatitis c patients applying to Katip Celebi University Ataturk Research and Training Hospital, Department of Gastroenterology between 01.01.2005 and 01.11.2012 with ages ranging from 20 to 75 years having pre- and post-treatment serum uric acid and HCV-RNA (0, 12, 24, 48 and 72 weeks) levels available were included in the study. These parameters were assessed according to the groups based on response to therapy (sustained virologic response -SVR, relapse and non- responders). Inclusion and exclusion criteria are as follows;

- Inclusion criteria: having diagnosed with chronic hepatitis c, completion of therapy
- Exclusion criteria: poor follow-up, chronic renal failure, any solid organ or hematologic malignancy, HIV positivity, pregnancy

Our study was performed in accordance with Helsinki Declaration. Ethics committee of University of Katip Celebi Ataturk Research and Training Hospital reviewed and consented the study.

Clinical and Laboratory Assessments

Patients' records including body weight, body mass index, waist circumference, uric acid, glucose, total cholesterol, triglyceride, HDL & LDL cholesterol, Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Gamma-Glutamyl Transpeptidase (GGT), creatinine, insulin levels, hematologic parameters, liver biopsy and upper abdominal ultrasonography reports were obtained via Probel patient recording system. Statistical analyses were performed.

Histologic Assessment

Pathologic samples were assessed by pathologists blind both to patients and histories. Adequate sample was defined as a biopsy material of more than 15 mm or at least 10 complete portal fields. Samples were classified with respect to Ishak system. Steatosis was defined as percentage of hepatocytes including fat droplets. Steatosis was stratified as "none", "mild", "mild to moderate" and "severe" corresponding to less than 5%, between 5-33%, 33-66% and more than 66%; respectively.

Antiviral Therapy Schedule

Patients were administered PEG-IFN 2a (Pegasys; Roche, Basel, Switzerland) as 180 mcg/week and ribavirin (1000 mg/day for those with a body weight of less than 75 kg and 1200 mg/day for more than 75 kg) during 48 weeks. Treatments were stopped unless "virologic response" defined as undetectable HCV-RNA via PCR at week 24 was achieved.

Statistical methods

Continuous variables were denoted by +/- while categorical ones were by frequency and percentage. ANOVA, t-test and chi-square tests were used appropriately. Multiple logistic regression model was used to assess independently associated factors with hyperuricemia, severe necroinflammatory activity, severe fibrosis and sustained virologic response. In the first

model, the dependent variable was "hyperuricemia" entered as 0 or 1 corresponding to "no" and "yes", respectively. It was "necroinflammatory activity" the dependent variable in the second model which was entered as 0 or 1 corresponding to "not severe (G0-G2)" and "severe (G3)", respectively. In the third model, the dependent variable was "fibrosis" entered as 0 or 1 meaning "not severe (F0-F2)" and "severe (F3-F4)", respectively. In the fourth one, the dependent variable was "sustained virologic response" that was entered as 0 or 1 meaning "no" and "yes", respectively. Besides, multiple ordinal regression models were used to assess independently associated factors with severity of liver steatosis.

Probable risk factors were determined as age, gender, body mass index, ALT, thrombocyte, total cholesterol, LDL, HDL, triglycerides, glucose, insulin, HOMA-IR score, arterial hypertension, diabetes mellitus, creatinine, eGFR (glomerular filtration rate - assessed in hyperuricemia model only), HCV-RNA (denoted by Log10), viral genotype, uric acid levels, hyperuricemia, steatosis, necroinflammatory activity and fibrosis.

HOMA-IR score, glucose, insulin, uric acid levels along with hyperuricemia were not included in the same model with ALT and necroinflammatory activity to avoid linear relationship effect. Regression analyses were conducted using sub-sofwares of PROC LOGISTIC, PROC REG and SAS.

RESULTS

Basic demographic data of our patients were shown in Table 1. Of the 165 patients, 63 were male and 102 were female. Mean age was 53,4 +/- 11,5. 28,5% (n=47) of the patients were normal-weight while 44,2% (n=73) were overweight and 27,3% (n=45) were obese. Cholesterol parameters (total cholesterol, triglyceride, LDL and HDL) were in normal range on average. HOMA-IR averages were quite higher than normal individuals as being 5,33 +/- 5,59. Diabetes mellitus, arterial hypertension, metabolic syndrome and hyperuricemia were not found in vast majority. It was genotype 1b the responsible agent in 154 (93,3%) patients while genotype 1a in 11 (6,7%). In 90,9% (n=150) of the patients, steatosis was detected and of these, 74% had mild steatosis while 16% moderate and 10% severe. Histologic activity index was 0 in 46 (30,7%) patients whereas 1 in 67 (44,7%) and 2 in 37 (n=24,7%). Stage of fibrosis was 0 in 14 (9,3%), 1 in 53 (n=35,3%), 2 in 43 (n=28,7%) and 3 in 40 (26,7%) patients.

Table 2 includes data regarding comparison of degree of steatosis and various parameters. Of the numerous parameters; only waist circumference, uric acid level and hyperuricemia were found to be statistically related to degree of steatosis when it was divided into three as "none" (steatosis in less than 5% of hepatocytes), "mild" (steatosis in between 5-30% of hepatocytes) and "severe" (steatosis in more than 30% of hepatocytes) (p values were 0,005; 0,002; 0,007; respectively).

We detected that waist circumference showed a significant association between "severe steatosis" and "no steatosis" groups only (groups 2 and 0) (p value 0,006) whereas uric acid did both between groups 0 - 1 and groups 0 - 2 (p values 0,044; 0,018; respectively) when steatosis groups were assessed with respect

Table 1: Basic demographic data of CHC patients.

	HCV (n=165)
Gender (M/F)	63/102
Age (years)	53,4 ± 11,5 (56; 21-71)*
Body Mass Index (kg/m ²)	27,65 ± 4,54 (27,1; 17,6-42,2)
Body Mass Index (kg/m ²)	
<25	47 (28,5)
25-29,9	73 (44,2)
≥30	45 (27,3)
Waist Circumference (cm)	97,02 ± 11,94 (97; 69-130)
AST (IU/L)	59,13 ± 47,69 (48; 14-480)
ALT (IU/L)	69,55 ± 49,54 (56; 13-373)
GGT (IU/L)	73,82 ± 69,51 (47; 10-350)
Platelet	209±72 (201; 21-440)
Total Cholesterol (mg/dL)	158,64 ± 33,89 (159; 76-246)
Triglyceride (mg/dL)	114,94 ± 58,51 (101; 23-400)
LDL-Cholesterol (mg/dL)	92,58 ± 33,45 (89; 22-220)
HDL-Cholesterol (mg/dL)	45,19 ± 14,71 (44; 15-106)
Fasting Blood Glucose (mg/dL)	108,49 ± 33,77 (98; 68-288)
Postprandial Glucose	158,50±95,63 (124; 66-591)
HbA1C	5,83±1,53 (5,5; 3,1-11,2)
Insulin (µU/mL)	18,57 ± 14,90 (13,70; 2,0-88,2)
HOMA-IR	5,33 ± 5,59 (3,42; 0,40-32,60)
Uric Acid	4,99 ± 1,55 (4,80; 2,1-10,9)
Diabetes Mellitus (Yes %/ No %)	39 (23,6) /126 (76,4)
Arterial Hypertension (Yes %/ No %)	38 (23)/127 (77)
Metabolic Syndrome (Yes %/ No %)	36 (21,8)/129(78,2)
Hyperuricemia (Yes %/ No %)	23/142
Viral genotype (1a /1b)	11/154
Log10 HCV-RNA	5,71±0,85 (5,74; 3,11-7,54)
Rapid Virologic Response	48/117
Early Virologic Response	94/71
Histology (n=150)	
Degree of Steatosis	n (%)
1 (5-33 %)	111 (74)
2 (>33-66%)	24 (16)
3 (>66%)	15 (10)
Histologic Activity Index	n (%)
0 (0)	46 (30,7)

1 (1-8)	67 (44,7)
2 (9-18)	37 (24,7)
Fibrosis Stage	n (%)
0 (0)	14 (9,3)
1 (1-2)	53 (35,3)
2 (3-4)	43 (28,7)
3 (5-6)	40 (26,7)

*Mean ± Standard Deviation (median; minimum-maximum)
 AST: Aspartate Aminotransferase, ALT: Alanine Aminotransferase, GGT: γ-glutamyltranspeptidase, LDL: Low-density Lipoprotein, HDL: High-density Lipoprotein HOMA-IR: Homeostasis model assessment of insulin resistance. Metabolic syndrome, ATP III criteria are defined as follows: waist circumference ≥ 102 cm and ≥ 88 cm for male and female respectively; blood pressure ≥130/85 mmHg or diagnosis of controlled hypertension under treatment; triglyceride ≥ 150 mg/dl; HDL < 40 and < 50 mg/dl for male and female, respectively; fasting plasma glucose ≥ 100 mg/dl or diagnosis of controlled diabetes mellitus under treatment

Table 2: Comparison of degree of steatosis and various parameters.

Variable	None	Mild	Severe	P value
	<%5 (n=111)	%5-30 (n=24)	>%30 (n=15)	
Gender (M/F)	41/70	13-Nov	9-Jun	0.715 [†]
Age -years	53,37±11,3	58,33±8,3	56,12±11,49	0.119
Body Mass Index-kg/m ²	27,3±4,5	28.0±3.6	28.9±4.7	0.05
Body Mass Index-kg/m ²				0.406 [†]
<25	34	4	3	
25-29,9	51	14	6	
≥30	26	6	6	
Waist Circumference (cm)	95.1±11.1	99.3±10.3	102.9±15.2	0.005*
Aspartate				
Aminotransferase - IU/L	60.9±50.5	53.4±31.9	84.1±86.9	0.614
Alanine Aminotransferase - IU/L	71.2±47.3	66.4±48.7	110±124.4	0.459
γ-glutamyl transpeptidase	69.5±67.1	80.3±54.7	97.9±92.7	0.131
Cholesterol - mg/dL	157.6±31.4	166.3±45.3	157.5±34.8	0.867*
Triglyceride - mg/dL	112.3±57.1	140.7±82.7	114.3±62.8	0.45
LDL - Cholesterol - mg/dL	91.1±31	96.5±39.9	92.5±33.3	0.771
HDL - Cholesterol- mg/dL	46.2±14.8	42.2±14.7	43.6±15.6	0.113
Blood Glucose- mg/dL	106.6±28.7	112.5±42.2	110±39	0.828
Insulin - µU/mL	17.7±13.6	20.7±18.9	15.9±11.2	0.979
HOMA	4.75±4.1	6.72±8.1	4,56±4.3	0.978

Uric Acid	4.72±1.3	5.42±1.5	5.9±2.1	0.002
Platelet	207.3±71.8	196.2±91.6	199.9±57.6	0.753*
Diabetes Mellitus (Yes / No)	25 /86	17-Jul	10-May	0.565 [†]
Arterial Hypertension (Yes / No)	23/88	16-Aug	11-Apr	0.395 [†]
Metabolic Syndrome (Yes / No)	21/90	18-Jun	9-Jun	0.168 [†]
Hyperuricemia (Yes %/ No)	Sep-91	17-Jun	9-May	0.007 [†]
Treatment (SVR/ NonSVR)	66/45	14-Oct	8-Jul	0.219 [†]
Viral genotype (1a /1b)	19/64	21/52	21/38	0,253 [†]
LogHCV-RNA	5.74±0.88	5.47±0.96	5.93±0.81	0.067*
Histology				
Histologic Activity Index				0.094 [†]
0 (0)	32	11	3	
1 (1-8)	54	7	5	
2 (9-18)	24	6	7	
Fibrosis				0.281 [†]
0 (0)	14	0	1	
1 (1-2)	38	10	5	
2 (3-4)	29	9	4	
3 (5-6)	29	5	6	

*Anova test; [†]Pearson chi-square; Others: Kruskal-Wallis

to three parameters between which a significant association was noted separately (Table 3). Similarly, hyperuricemia showed a significant association between groups 0 - 1 along with groups 0 - 2 (p values 0,031 and 0,019; respectively).

No significant association was found between degree of steatosis and sustained virologic response, histologic activity index and fibrosis (p values 0,219; 0,094 and 0,281; respectively).

No significant association was found between fibrosis and uric acid levels, existence of hyperuricemia and degree of steatosis (p values 0,657; 0,235 and 0,281; respectively).

Of the 165 patients, 28 were excluded from hyperuricemia analyses owing to lack of uric acid levels and/or liver biopsies. Of the 137 included, 117 had no hyperuricemia while 20 did (cut-off levels were 7 and 6 mg/dL in males and female, respectively). In uni-variate analyses, no statistically significant association was established between hyperuricemia and age, waist circumference, HOMA-IR score, sustained virologic response, fibrosis and histologic activity index (table 4) (p values were 0,61; 0,115; 0,437; 0,645; 0,235 and 0,166; respectively). However, significant association was found between hyperuricemia and body mass index, hypertension, existence of metabolic syndrome and grade of steatosis (p values were 0,045; 0,04; 0,045; 0,007;

respectively) (table 4). No significant relevance was noted between hyperuricemia and the parameters in multivariate analyses (Table 5).

DISCUSSION

Hepatitis C infection is one of crucial causes of chronic liver diseases. Recently, influence of some factors such as insulin resistance and steatosis on chronic hepatitis C infection has been handled [11,12]. Besides, these factors have also been shown to be associated with non-alcoholic fatty liver disease [13]. Some evidence advocating influence of aforementioned factors on the therapy has emerged [10,14].

Relationship between gout disease and hypertension, diabetes mellitus, renal and cardiovascular diseases have long been known [15-18]. In recent years, this relationship has also been shown in metabolic syndrome, coronary artery disease, cerebrovascular disease, dementia and preeclampsia [15-20]. Some culprit mechanisms include low glomerular filtration rate, renal vasoconstriction, alcohol use, ischemic events, oxidative stress [21]. Besides, an independent association was found between uric acid levels and histology of non-alcoholic fatty

Table 3: Associations between degree of steatosis and some parameters.

	Group 0- 1	Group 0- 2	Group 1- 2
Body Mass Index	0.237	0.173	0.757
Waist Circumference	0.259	0.006*	0.356
Uric Acid	0.044	0.018	0.414
Hyperuricemia	0.031	0.019	0.707

Table 4: Regression analysis between uric acid and other parameters.

	Uric Acid	
	R	p
Age	0,148	0,068
Body Mass Index	0,213	0,009
Waist Circumference (cm)	0,228	0,020
Aspartate Aminotransferase IU/L	-0,052	0,528
Alanine Aminotransferase - IU/L	-0,010	0,907
γ-glutamyl transpeptidase	0,127	0,119
Cholesterol - mg/dL*	-0,028	0,730
Triglyceride- mg/dL	0,170	0,036
LDL - Cholesterol - mg/dL	0,002	0,984
HDL - Cholesterol - mg/dL	-0,277	0,001
Blood Glucose- mg/dL	-0,124	0,128
Insulin - µU/mL	0,016	0,852
HOMA	-0,041	0,629
Log10 HCV-RNA*	0,060	0,465
Platelet	-0,019	0,812
Steatosis Degree	0,295	<0,001
Histologic Activity Index	0,168	0,049
Fibrosis	0,038	0,657

Table 5: Uni-and multivariate comparisons between patients with and without hyperuricemia.

Variable	Hyperuricemia None (n=117)	Hyperuricemia Yes (n=20)	Univariate Analysis (p)	Multivariate Analysis (OR% 95 CI)	P
Age (years)	53,29 ± 11,3 (56)*	57 ± 10,9 (57)	0,163	1,015 (0,959-1,075)	0,610
Body Mass Index (kg/m ²)	27,18 ± 4,58 (26,6)	28,65 ± 3,29 (28,4)	0,045	1,063 (0,947-1,193)	0,300
Body Mass Index (kg/m ²)			0,114		
<25	38	2			
25-29,9	52	11			
≥30	27	7			
Waist Circumference (cm)	98,18 ± 5,85 (98)	101,19 ± 7,51 (100)	0,115		
AST (IU/L)	60,66 ± 53,94 (47)	55,45 ± 24,09 (55)	0,604		
ALT (IU/L)	69,66 ± 53,09 (54)	77,35 ± 45,63 (74)	0,216		
GGT (IU/L)	75,47±73,53 (46)	69,80 ± 43,75 (57)	0,367		
Total Cholesterol (mg/dL)	157,32 ± 35,14 (157)	165,95 ± 30,55 (166)	0,304		
Triglyceride (mg/dL)	113,62 ± 64,09 (96)	125,55 ± 34,25 (122)	0,028	1,002 (0,993-1,012)	0,616
LDL-Cholesterol (mg/dL)	91,89 ± 35,09 (90)	98,75 ± 29,92 (89)	0,387		
HDL-Cholesterol (mg/dL)	45,52 ± 15,36 (44)	42,30 ± 11,51 (41)	0,421	0,998 (0,952 - 1,047)	0,949
Fasting Blood Glucose (mg/dL)	111,06 ± 37,1 (98)	98 ± 14,2 (97)	0,369		
Insulin (µU/mL)	17,94 ± 14,44 (13,6)	23,39 ± 17,67 (17,9)	0,151		
HOMA-IR	5,22 ± 5,36 (3,42)	5,81 ± 5,18 (4,78)	0,437	0,988 (0,885-1,103)	0,832
Platelet	209,3 ± 75,4 (198)	181,2 ± 58,5 (182,5)	0,115		
Log10_HCVRNA	5,72±0,73 (5,73)	5,90±0,91 (6,1)	0,321		
Diabetes Mellitus (Yes / No)	34/83	2/18	0,074		
Arterial Hypertension (Yes / No)	27/90	9/11	0,040	2,383 (0,453-12,542)	0,306
Metabolic Syndrome (Yes / No)	23/94	8/12	0,045	1,162(0,177-	0,876

liver disease [22]. In this context, some studies were performed handling the association between uric acid levels and hepatitis C infection [10,23, 24]. Grassi, et.al. Showed that steatosis was found in 66,1% of CHC patients and that steatosis well correlated with uric acid, body mass index and GGT levels [23]. In a recent study, it was noted that steatosis was more severe if hyperuricemia was detected (OR= 3,176) and that hyperuricemia frequency was markedly high if steatosis existed (OR= 2,751). A significant association was also found between severity of steatosis and uric acid levels, body mass index, triglycerides, HOMA-IR score, genotype 3 infection and necroinflammatory activity in the same study. In parallel with the literature, although lack in numbers, we found a significant correlation between steatosis and uric acid levels as the greater degree of steatosis the greater the number of hyperuricemic patients. Different than literature, we found significant correlation between steatosis and LDL, HDL plus histologic activity index along with body mass index and uric acid level but triglycerides and HOMA-IR score. The reason of this discrepancy might be our group to be composed of genotype 1 patients only, high number of overweight and obese patients or paucity of patients with high-grade steatosis. On the other hand, adiponectin levels were found low in CHC patients [25]. Besides,

in patients with non-alcoholic fatty liver disease, uric acid was found high while adiponectin was low [22]. This discrepancy may be related to metabolic pathway in CHC patients to be different.

Association between uric acid levels and metabolic syndrome has been shown [26]. High uric acid levels seen in patients with metabolic syndrome may cause hyperinsulinemia. Besides, hyperuricemia usually precedes hyperinsulinemia, obesity and diabetes mellitus [21]. There are a few theories about this; first, hyperuricemia may cause metabolic syndrome by endothelial dysfunction [27]; second, uric acid may cause metabolic syndrome by making some inflammatory and oxidative alterations on adipocytes [28]. There exists very few data on uric acid levels and metabolic factors in CHC patients in literature. In this study, being different than others, frequency of metabolic syndrome and arterial hypertension was higher in hyperuricemic group. However, no significant difference was noted between hyperuricemic and normouricemic CHC patients in terms of insulin, glucose and HOMA-IR scores. This may be related to different metabolic pathways take place in development of metabolic syndrome in hepatitis C patients. Molecular studies are required to enlighten this issue.

It has been noted in literature that many factors including age, viral load, body mass index and insulin resistance may play a role in progression of fibrosis in patients with CHC [29]. However, studies handling association between uric acid and fibrosis are lacking. In a study conducted by Afzali et al., a significant association was found between uric acid levels and cirrhosis in chronic liver patients [30]. However, Petta et al did not find any relation between uric acid and fibrosis in CHC patients [24]. In this study, we did not note any association between uric acid levels and fibrosis plus histologic activity index. This may be related to abundance of factors playing a role in development of fibrosis in hepatitis C patients.

Sustained virologic response can be achieved in more than 50% of patients with PEG- INF plus ribavirin therapy in CHC. Treatment success can be influenced by numerous factors including genotype, viral load, age, gender, weight, insulin resistance and metabolic syndrome [31,32]. Petta et al could not find any relation between uric acid levels and sustained virologic response rates [24]. We achieved a SVR rate of 55,2%. Similar to the literature, no significant difference was noted between hyperuricemic and normouricemic patients in terms of SVR rates. When compared SVR to non-SVR group, no significant difference was shown in uric acid levels. In parallel with the study of Petta et al., although low subject number, it can be inferred that uric acid level has no influence on therapy success in CHC patients. How can this be explained?

Infected cells are cleared by Th-1 cell immune response in CHC infection [33]. Uric acid may prevent cell damage by stimulating nitric acid synthase enzyme [34,35]. Besides, interferon may also stimulate nitric acid synthase enzyme [36].

High uric acid levels may protect infected cell against Th-1 cell immune response. In opposite, low serum uric acid levels may cause a more potent Th-1 immune response against infected cells [10]. A third hypothesis to these two is the TNF-alfa synthesis with purine pathway. Schulz et al reported a positive correlation between TNF-alfa and uric acid levels [37]. High TNF-alfa levels lower success rates of antiviral therapy [38]. Despite these theories, no sufficient clarification has been documented regarding the relation between uric acid levels and therapy response in literature to date. Differences in host immune response such as IL28b genetic polymorphism may clarify this. Further multi-center studies handling IL28 genetic polymorphism including HCV patients with different genotype are needed.

CONCLUSION

There has been found a significant association between uric acid levels and steatosis in CHC patients. This study did not reveal any influence of uric acid level on success of therapy. Further multi-center studies are required to clarify this metabolic chaos.

REFERENCES

- Marcellin P. Management of Patients with Viral Hepatitis, 2007 APHC, Paris France.
- Akhan S. Hepatit C virüsü. Topçu AW, Söyletir G, Doğanay M (editörler). *İnfeksiyon Hastalıkları Mikrobiyolojisi*. İstanbul: Nobel Tıp Kitabevleri. 2008:1911-1929.
- Chou R, Clark EC, Helfand M. Screening for hepatitis C virus infection. A review of the evidence for the US preventive services task force. *Ann Intern Med*. 2004; 140: 465-479.
- Consensus conference. Treatment of hepatitis C. Guidelines. *Gastroenterol Clin Biol*. 2002; 26: B312-B320.
- Fried MW, Shiffman ML, Reddy KR, Smith C, Marinos G, Gonçalves Jr FL, et al. Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med*. 2002; 347: 975-982.
- Cornberg M, Manns MP, Wedemeyer H. Hepatitis C, standard of care. In: Mauss S, Berg T, Rockstroh J, Sarrazin C, Wedemeyer H (eds). *Hepatology. A Clinical Textbook*. Germany: Flying Publisher. 2009: 183-198.
- Grace MJ, Bordens RW, Cutler DL. Peginterferons for the treatment of chronic hepatitis C. *Hepatology Rev*. 2005; 2: 3-9.
- Aspinall RJ, Pockros PJ. Review article: The management of side effects during therapy for hepatitis C. *Aliment Pharmacol Ther*. 2004; 20: 917-929.
- Fried MW. Side effects of therapy of hepatitis C and their management. *Hepatology*. 2002; 36 (5 Suppl 1): 237-244.
- Pellicano R, Puglisi G, Ciancio A, Balzola F, Saracco G, Ciccone G, et al. Is serum uric acid a predictive factor of response to IFN-treatment in patients with chronic hepatitis C infection?. *J Med Virol*. 2008; 80: 628-631.
- Aghemo A, Prati GM, Rumi MG, Soffredini R, D'Ambrosio R, Orsi E, et al. Sustained virological response prevents the development of insulin resistance in patients with chronic hepatitis C. *Hepatology*. 2012; 56: 1681-1687.
- Cammà C, Bruno S, Di Marco V, Di Bona D, Rumi M, Vinci M, et al. Insulin resistance is associated with steatosis in nondiabetic patients with genotype 1 chronic hepatitis C. *Hepatology*. 2006; 43: 64-71.
- Petta S, Muratore C, Craxi A. Non-alcoholic fatty liver disease pathogenesis: the present and the future. *Dig Liver Dis*. 2009; 41: 615-625.
- Romero-Gómez M, Del Mar Vitoria M, Andrade RJ, Salmerón J, Diago M, Fernández-Rodríguez CM, et al. Insulin resistance impairs sustained response rate to peginterferon plus ribavirin in chronic hepatitis C patients. *Gastroenterology*. 2005; 128: 636-641.
- Dyer AR, Liu K, Walsh M, Kiefe C, Jacobs DR Jr, Bild DE. Ten-year incidence of elevated blood pressure and its predictors: the CARDIA study. *J Hum Hypertens*. 1999; 13: 13-21.
- Krishnan E, Kwok CK, Schumacher HR, Kuller L. Hyperuricemia and incidence of hypertension among men without metabolic syndrome. *Hypertension*. 2007; 49: 298-303.
- Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care*. 2008; 31: 361-362.
- Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int*. 2005; 67: 1739-1742.
- Schretlen DJ, Inscore AB, Vannorsdall TD, Kraut M, Pearson GD, Gordon B, et al. Serum uric acid and brain ischemia in normal elderly adults. *Neurology*. 2007; 69: 1418-1423.
- Siu YP, Leung KT, Tong MK, Kwan TH. Use of allopurinol in slowing the progression of renal disease through its ability to lower serum uric acid level. *Am J Kidney Dis*. 2006; 47: 51-59.
- Quiñones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, et al. Effect of insulin on uric acid excretion in humans. *Am J Physiol*. 1995; 268: E1-E5.

22. Petta S, Cammà C, Cabibi D, Di Marco V, Craxi A. Hyperuricemia is associated with histological liver damage in patients with non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2011; 34: 757-766.
23. Grassi A, Ballardini G, Susca M, Bianchini F, Bonoli S, Bianchi FB, Lenzi M. HCV liver infection and liver steatosis: evidence for indirect mechanisms in genotype 3? *Aliment Pharmacol Ther.* 2005; 22: Suppl 2: 79-82.
24. Petta S, Macaluso FS, Cammà C, Marco VD, Cabibi D, Craxi A. Hyperuricaemia: another metabolic feature affecting the severity of chronic hepatitis because of HCV infection. *Liver Int.* 2012; 32: 1443-1450.
25. Chen L, Liu W, Lai S, Li Y, Wang X, Zhang H. Insulin resistance, serum visfatin, and adiponectin levels are associated with metabolic disorders in chronic hepatitis C virus-infected patients. *Eur J Gastroenterol Hepatol.* 2013; 25: 935-941.
26. Feig DI, Kang DH, Johnson RJ. Uric acid and cardiovascular risk. *N Engl J Med.* 2008; 359: 1811-1821.
27. Cook S, Hugli O, Egli M, Vollenweider P, Burcelin R, Nicod P, et al. Clustering of cardiovascular risk factors mimicking the human metabolic syndrome X in eNOS null mice. *Swiss Med Wkly.* 2003; 133: 360-363.
28. Sautin YY, Nakagawa T, Zharikov S, Johnson RJ. Adverse effects of the classical antioxidant uric acid in adipocytes: NADPH oxidase-mediated oxidative/nitrosative stress. *Am J Physiol Cell Physiol.* 2007; 293: C584-C596.
29. Poynard T, Bedossa P, Opolon P. Natural history of liver fibrosis progression in patients with chronic hepatitis C. The OBSVIRC, METAVIR, CLINIVIR, and DOSVIRC groups. *Lancet.* 1997; 349: 825-832.
30. Afzali A, Weiss NS, Boyko EJ, Ioannou GN. Association between serum uric acid level and chronic liver disease in the United States. *Hepatology.* 2010; 52: 578-589.
31. Chalasani N, Younossi Z, Lavine JE, Diehl AM, Brunt EM, Cusi K, Charlton M, Sanyal AJ; American Association for the Study of Liver Diseases; American College of Gastroenterology; American Gastroenterological Association. The diagnosis and management of non-alcoholic fatty liver disease: Practice guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. *Am J Gastroenterol.* 2012 ; 107: 811-826.
32. European Association for the Study of the Liver. EASL Clinical Practice Guidelines: management of hepatitis C virus infection. *J Hepatol.* 2011; 55: 245-264.
33. Thomas HC, Török ME, Forton DM, Taylor-Robinson SD. Possible mechanisms of action and reasons for failure of antiviral therapy in chronic hepatitis C. *J Hepatol.* 1999; 31Suppl 1:152-159.
34. Hooper DC, Spitsin S, Kean RB, Champion JM, Dickson GM, Chaudhry I, Koprowski H. Uric acid, a natural scavenger of peroxynitrite, in experimental allergic encephalomyelitis and multiple sclerosis. *Proc Natl Acad Sci U S A.* 1998; 95: 675-680.
35. Tsukada K, Hasegawa T, Tsutsumi S, Katoh H, Kuwano H, Miyazaki T, et al. Effect of uric acid on liver injury during hemorrhagic shock. *Surgery.* 2000; 127: 439-446.
36. Oh I, Ozaki K, Sato K, Meguro A, Tatara R, Hatanaka K, et al. Interferon-gamma and NF-kappaB mediate nitric oxide production by mesenchymal stromal cells. *Biochem Biophys Res Commun.* 2007; 355: 956-962.
37. Schulz S, Schagdarsurengin U, Suss T, Müller-Werdan U, Werdan K, Gläser C. Relation between the tumor necrosis factor-alpha (TNF-alpha) gene and protein expression, and clinical, biochemical, and genetic markers: age, body mass index and uric acid are independent predictors for an elevated TNF-alpha plasma level in a complex risk model. *Eur Cytokine Netw.* 2004; 15: 105-111.
38. Dumoulin FL, Wennrich U, Nischalke HD, Leifeld L, Fischer HP, Sauerbruch T, et al. Intrahepatic mRNA levels of interferon gamma and tumor necrosis factor alpha and response to antiviral treatment of chronic hepatitis C. *J Hum Virol.* 2001; 4: 195-199.

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